HEPATITIS C
JUNE 2003

1: Aids Alert. 2003 May;18(5):63-5.
Coalition seeks funding for HCV/HIV co-infection. Integrating services makes economic, medical sense.
[No authors listed]
With Hepatitis C virus infecting up to 40% of HIV-positive patients, liver disease has become the leading cause of death in AIDS patients. And yet funding for hepatitis screening and treatment is inadequate, and states must use creative strategies to integrate HCV screening into existing HIV services.
Publication Types:
Newspaper Article
PMID: 12751456 [PubMed - indexed for MEDLINE]

2: Am J Epidemiol. 2003 Apr 15;157(8):674-82.
Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan.
Sun CA, Wu DM, Lin CC, Lu SN, You SL, Wang LY, Wu MH, Chen CJ.
School of Public Health, National Defense Medical Center, Taipei, Taiwan. sunca@ndmctsgh.edu.tw
In a community-based prospective study, the authors examined the independent and interactive effects of hepatitis C virus (HCV) infection and cofactors, including hepatitis B virus (HBV) infection and lifestyle habits, on the incidence of hepatocellular carcinoma (HCC) in Taiwan. At baseline recruitment, subjects were evaluated with regard to second-generation HCV antibody (anti-HCV), hepatitis B surface antigen, and serum alanine aminotransferase, as
well as cigarette smoking, alcohol drinking, and betel quid chewing habits. A total of 12,008 male residents aged 30-64 years without a history of HCC were included in the study. Between July 1990 and June 2001, 112 incident cases of HCC were identified among the subjects and included in the analysis. Persons with anti-HCV positivity alone had a 20-fold increased risk of developing HCC in comparison with those who were negative for anti-HCV. In statistical assessment of additive interaction, HCV and HBV tended to act independently in the pathogenesis of HCC. The results of this study suggest that HCV plays a significant role in hepatocarcinogenesis in an area endemic for chronic HBV infection.
PMID: 12697571 [PubMed - indexed for MEDLINE]

3: Ann Rheum Dis. 2003 May;62(5):388-93.
Antiphospholipid antibodies and infections.
Asherson RA, Cervera R.
Rheumatic Diseases Unit, Department of Medicine, University of Cape Town School of Medicine and Groote Schuur Hospital, Cape Town, South Africa.
Many infections have been found to be associated with antiphospholipid antibodies (aPL), although a pathogenic role for these antibodies has not usually been obvious

except in a few isolated cases. Two types of aPL have been referred to as "autoimmune" and "infectious" types. This distinction, however, has subsequently been found not to be absolute.
Publication Types:
Review
Review, Tutorial
PMID: 12695147 [PubMed - indexed for MEDLINE]

4: Arch Intern Med. 2003 May 12;163(9):1095-8.
The tattooing paradox: are studies of acute hepatitis adequate to identify routes of transmission of subclinical hepatitis C infection?
Haley RW, Fischer RP.
Epidemiology Division, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8874, USA. Robert.Haley@UTSouthwestern.edu
BACKGROUND: The Hepatitis Branch of the Centers for Disease Control and Prevention does not recommend routine regulation and inspection of tattoo parlors because surveillance of hepatitis C virus (HCV)-positive acute hepatitis cases rarely identifies tattooing in the incubation period. However, the majority of seroepidemiological studies agree that tattooing is a strong, independent risk factor for subclinical HCV seropositivity. We postulated that this paradox might be explained if transmission of HCV by tattooing generally caused subclinical HCV seropositivity without the acute hepatitis syndrome. METHODS: We reanalyzed data from a prior seroepidemiological study of 626 consecutive patients who were unaware of their HCV serologic status and whose risk factors were ascertained by interview of an internist. Separate multiple logistic regression models were developed to predict a history of the acute hepatitis syndrome and HCV seropositivity. RESULTS: A history of injection-drug use was strongly associated with both HCV seropositivity (adjusted odds ratio [AOR], 7.2; 95% confidence interval [CI], 3.1-16.5) and a history of acute hepatitis (AOR, 5.9; 95% CI, 2.5-13.8), whereas having a commercially applied tattoo was strongly associated with HCV seropositivity (AOR, 6.5; 95% CI, 2.9-14.4) but not with a history of acute hepatitis (AOR, 1.2; 95% CI, 0.5-3.3).
CONCLUSIONS: Intravenous injection of relatively large quantities of innocula of HCV may be more likely to result in the relatively rare acute HCV hepatitis syndrome, whereas intradermal exposure to small quantities of innocula may cause only subclinical HCV infections. If so, public policy on regulation and inspection of tattoo parlors should be determined by seroepidemiological studies rather than by the Sentinel Counties Study of acute hepatitis cases.
PMID: 12742809 [PubMed - indexed for MEDLINE]

5: Cancer. 2003 May 15;97(10):2474-9.
Identification of the antigens predominantly reacted with serum from patients with hepatocellular carcinoma.
Uemura M, Nouso K, Kobayashi Y, Tanaka H, Nakamura S, Higashi T, Ono T, Nakayama
E, Hanafusa T, Shiratori Y.
Department of Medicine and Medical Science, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan.
BACKGROUND: To identify antigens specifically recognized by the immune surveillance system in patients with hepatocellular carcinoma (HCC), the authors examined two complementary DNA (cDNA) libraries of moderately differentiated HCC by serologic analysis of recombinant cDNA expression libraries (SEREX). METHODS:

The libraries were screened with autologous patients' sera, and sequences of the reacted clones were determined. To study the immunoreactivity of the antigens, sera from 20 patients with HCC, from 20 healthy volunteers, and from 16 patients with chronic viral hepatitis were examined. RESULTS: Twenty-seven antigens were identified. They included SART1, p57Kip2, ROCK-1, gamma-catenin, and heat shock proteins, which are classified as tumor-associated genes. Three of 27 antigens-Tat-binding protein-1 (TBP-1), beta4 integrin-binding protein (p27[BBP]), and ribosomal protein L30 (rpL30)-were reacted predominantly with sera from patients with HCC (55% of patients, 45% of patients, and 20% of patients, respectively). Patients in the control group had no antibodies against these three antigens. Seventy percent of patients with HCC had the antibody against at least one of these antigens. CONCLUSIONS: Disease specific humoral immune response against TBP-1, p27(BBP), and rpL30 was induced in patients with HCC, and the antibodies against these antigens also may be used as tumor markers. Copyright 2003 American Cancer Society.DOI 10.1002/cncr.11374
PMID: 12733146 [PubMed - indexed for MEDLINE]

6: Hepatology. 2003 May;37(5):1180-8.
Comment in:
Hepatology. 2003 May;37(5):975-8.
Gene expression associated with interferon alfa antiviral activity in an HCV replicon cell line.
Zhu H, Zhao H, Collins CD, Eckenrode SE, Run Q, McIndoe RA, Crawford JM, Nelson DR, She JX, Liu C.
Department of Pathology, Immunology, and Laboratory Medicine, University of Florida College of Medicine, Gainesville 32610, USA.
Interferon alfa (IFN-alpha)-based treatment is the only therapeutic option for chronic hepatitis C viral infection. However, the molecular mechanisms of IFN-alpha antiviral activity are not completely understood. The recent development of an HCV replicon cell culture system provides a feasible experimental model to investigate the molecular details of IFN-induced direct
antiviral activity in hepatocytes. In this report, we show that IFN-alpha can effectively inhibit HCV subgenomic RNA replication and suppress viral nonstructural protein synthesis. Using cDNA microarray analysis, we also show that the replicon cells have different gene expression profile compared with the parental hepatoma cells (Huh7). IFN-alpha can induce a number of responsive genes in the replicon cells. One of the genes, 6-16 (G1P3), can enhance IFN-alpha antiviral efficacy. In addition, we demonstrate that IFN-alpha can significantly activate STAT3 in hepatoma cells, suggesting that this pathway plays a role in IFN-alpha signaling. In conclusion, our results indicate that IFN-alpha antiviral activity is associated with activation of STAT3-signaling pathway and intracellular gene activation. Our results also suggest that IFN-alpha-induced target genes may play an important role in IFN-alpha anti-HCV activity.
PMID: 12717400 [PubMed - indexed for MEDLINE]

7: Hepatology. 2003 May;37(5):1189-98.
Detection of functionally altered hepatitis C virus-specific CD4 T cells in acute and chronic hepatitis C.
Ulsenheimer A, Gerlach JT, Gruener NH, Jung MC, Schirren CA, Schraut W, Zachoval R, Pape GR, Diepolder HM.
Institute for Immunology, University of Munich, Germany.
Chronic hepatitis C is characterized by a weak or absent hepatitis C virus (HCV)-specific CD4(+) T-cell response in terms of antigen-specific proliferation or interferon gamma (IFN-gamma) secretion. To clarify whether this is due to the absence or functional impairment of antigen-specific CD4(+) T cells we developed an assay that

relies on the induced expression of the T-cell activation marker CD25 and is therefore independent from cytokine secretion or proliferation. In 10 of 20 patients with chronic hepatitis C, a significant number of antigen-specific activated CD4(+) T cells (mean 1.06%/patient; range, 0% to 5.2% of CD4(+) T cells) could be shown, whereas antigen-specific proliferation was present in only 1 of 20 patients. IFN-gamma secretion was absent in all 13 patients tested. However, significant antigen-specific interleukin 10 (IL-10) and transforming growth factor beta (TGF-beta) secretion was present in 6 of 10 and 3 of 10 patients, respectively. In 8 patients with acute hepatitis C, irrespective of disease outcome, HCV-specific CD4(+) T cells were detected in all patients and at a significantly higher frequency (mean 3.7%/patient; range, 1.16% to 7.17%) in the first weeks of disease. A chronic course of disease was associated either with a loss of both IFN-gamma secretion and proliferation, resembling an anergic state, or a loss of T-cell proliferation followed by a rapid decline in IFN-gamma-producing cells, corresponding to exhaustion of the specific immune response. In conclusion, functional changes of HCV-specific CD4(+) T cells or failure to develop a long-lasting T-helper response may contribute to chronic hepatitis C viral persistence.
PMID: 12717401 [PubMed - indexed for MEDLINE]

8: J Infect Dis. 2003 Apr 15;187(8):1264-71. Epub 2003 Apr 02.
Association of CTLA4 polymorphisms with sustained response to interferon and ribavirin therapy for chronic hepatitis C virus infection.
Yee LJ, Perez KA, Tang J, van Leeuwen DJ, Kaslow RA.
Program in Epidemiology of Infection and Immunity, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham Liver Center, University of Alabama at Birmingham, Birmingham, Alabama, USA.
Cytotoxic T lymphocyte antigen-4 (CTLA4) suppresses cytotoxic T lymphocyte activity. We examined the associations of CTLA4 single-nucleotide polymorphisms (SNPs) at promoter site -318 and exon-1 site 49 with clearance of hepatitis C virus (HCV) after treatment with combination interferon-alpha plus ribavirin (IFN-alpha+R) therapy in 79 white sustained responders (SRs) and 79 nonresponders (NRs). SRs had higher frequencies of 49G, alone (odds ratio [OR], 2.3; P=.042) and tightly linked with -318C in a haplotype (OR, 2.4; P=.030).
Homozygosity for the -318C-49G haplotype was even more frequent among SRs (OR,
5.2; P=.049). Comparably strong associations persisted after multivariable analysis. Relationships were not seen with non-1 genotype viruses (OR, 0.93-1.25; P>.25). Virus load also declined more rapidly in carriers of both 49G (P=.0095) and the -318C-49G haplotype. CTLA4 49G in exon 1 alone and in a haplotype with -318C promoter is associated with sustained IFNalpha+R response in white patients with HCV genotype 1 infection.
Publication Types:
Clinical Trial
PMID: 12696006 [PubMed - indexed for MEDLINE]

9: Transplantation. 2003 Apr 27;75(8):1396-9.
Steroid-free liver transplantation using rabbit antithymocyte globulin and early tacrolimus monotherapy.
Eason JD, Nair S, Cohen AJ, Blazek JL, Loss GE Jr.
Section of Abdominal Transplantation, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121, USA.
BACKGROUND: In 2001, we published early results of a prospective randomized trial of 71 patients who received either steroids or rabbit antithymocyte globulin (RATG) for orthotopic liver transplantation (OLT). We now report follow-up on these patients and additional patients undergoing steroid-free OLT. METHODS: A total of

119 adult OLT recipients were prospectively randomized to receive either methylprednisolone 1,000 mg followed by a 3-month steroid taper or a steroid-free regimen of RATG 1.5 mg/kg during the anhepatic phase followed by a 1.5 mg/kg dose on posttransplant day 1. Maintenance immunosuppression consisted of tacrolimus and mycophenolate mofetil in both groups. Mycophenolate mofetil was weaned over 3 months in the first 71 patients and over 2 weeks in the last 48 patients, achieving tacrolimus monotherapy by 2 weeks posttransplant. Subsequently, a group of 24 sequential OLT recipients received the steroid-free (RATG) protocol. Endpoints of the study were survival, rejection, infectious complications, posttransplant diabetes, and recurrent hepatitis C virus. RESULTS: One-year patient survival was 85% in each group of the prospective randomized trial with a mean follow-up of 18.5 months. One-year graft survival was 82% in the RATG group and 80% in the steroid group (P=not significant). Patient and graft survival of the 24 nonrandomized RATG patients was 96% with a mean follow-up of 3 months. The incidence of rejection was not significantly different; however, 50% of the patients in the steroid group required pulse steroids to reverse the rejection compared with only one patient (1.6%) in the RATG group (P=.03). The incidence of cytomegalovirus infection (P<.05) and posttransplant diabetes was higher in the steroid group (P=.03). There was a trend toward decreased severity of hepatitis C virus in the RATG group. CONCLUSIONS: Steroid-free liver transplantation using RATG and early tacrolimus monotherapy effectively reduces immunosuppression-related complications with excellent survival.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 12717237 [PubMed - indexed for MEDLINE]

10: Transplantation. 2003 Apr 15;75(7):977-82.

Effects of ursodeoxycholic acid (ursodiol) treatment on chronic viral hepatitis in heart transplant patients: results of a prospective, double-blind, placebo-randomized study.

Cadranel JF, Di Martino V, Dorent R, Bernard B, Hoang C, Myara A, Pauwels A, Ghoussoub JJ, Perrin M, Grippon P, Thabut D, Trivin F, Huraux JM, Gandjbakhch I, Opolon P, Lunel F.

Unite d'Hepatologie, Centre Hospitalier Laennec, BP 72, 60109 Creil Cedex, France. jfrancois.cadranel@ch-creil.fr

BACKGROUND: Chronic viral hepatitis averages 15% to 20% in heart transplant patients. Several studies have shown that ursodiol may improve liver biochemistry in patients with chronic hepatitis. We used a double-blind randomized controlled trial to evaluate the effect of ursodiol in heart transplant patients with chronic viral hepatitis. METHODS: Thirty heart patients with chronic viral hepatitis B, C, or non-A-G received ursodiol, 800 mg per day (group 1), and 30 received placebo (group 2) for 12 months. Endpoints were improvement in liver biochemical tests and in total Knodell score. Intent-to-treat and per-protocol analyses were performed. RESULTS: At entry, both groups were comparable for all of the studied parameters. During the study period, serum alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transpeptidase variations were not different between group 1 and group 2 patients. Knodell score improved in 20% of group 1 patients and in 43% of group 2 patients (NS). Adverse events or mortality were not different in the two groups during the study period. Similar results were observed by intent-to-treat and per-protocol analyses. CONCLUSIONS: A 12-month course of ursodiol therapy had no effect on liver enzymes or liver histology in heart transplant patients with chronic hepatitis.

Publication Types:
Clinical Trial
Randomized Controlled Trial
PMID: 12698083 [PubMed - indexed for MEDLINE]

11: Transplantation. 2003 Apr 15;75(7):982-6.
Natural leukocyte interferon alfa for the treatment of chronic viral hepatitis in heart transplant recipients.
Fagiuoli S, Pevere S, Minniti F, Livi U, Caforio AL, Naccarato R, Chiaramonte M.
Gastroenterology, Department of Surgical and Gastroenterological Sciences, University of Padua, Via Giustiniani 2, 35128 Padua, Italy. fagiuoli@unipd.it
BACKGROUND: A more rapid and aggressive course of hepatitis B virus (HBV)-related and hepatitis C virus (HCV)-related infection in organ transplant recipients has been described. Interferon alfa is the most accepted drug for treating HBV and HCV chronic infections. However, the use of interferon alfa-N3 has been contraindicated in heart transplant (HTx) recipients because of the hypothesized greater risk of triggering acute cellular rejection. The aim of
this clinical pilot study was to evaluate tolerability, safety, and efficacy of natural leukocyte interferon alfa in the treatment of chronic HBV and HCV in HTx recipients. METHODS: Seven HTx recipients were enrolled in the study: two with HBV, four with HCV, and one with combined HBV-HCV chronic infection. The patients had a mean follow-up after heart transplantation of 8.5+/-3 years, before starting interferon alfa-N3 treatment at a dose of 6 MU three times per
week, intramuscularly for 12 months. RESULTS: All patients completed the treatment with no major side effects. No unexpected episodes of acute cellular rejection were observed during the treatment. Mean aminotransferase serum levels were significantly lower than before transplantation at 3 ($P<0.03$), 6 ($P<0.02$), and 12 ($P<0.02$) months of treatment and at the 12-month follow-up ($P<0.02$). A complete and sustained response was achieved in all subjects with HBV-related chronic hepatitis, whereas sustained virologic response was observed in one of four HCV patients. CONCLUSIONS: The preliminary data emerging from our study indicate that natural leukocyte interferon alfa-N3 can be safely administered in HTx recipients with chronic HBV or HCV viral hepatitis. Further studies with larger numbers of patients are needed to assess the efficacy of interferon alfa-N3 on HCV virologic response.
PMID: 12698084 [PubMed - indexed for MEDLINE]